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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/230,929	04/02/1999	JURGEN KLEINSCHMIDT	4121-107	3634

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/230,929	KLEINSCHMIDT ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 14, 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-25,27,29,38-51,53-61,65 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-25,27,29,38-51,53-61,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application is a 371 national stage filing of PCT/DE97/01629, filed July 30, 1997, which claims benefit to foreign application 196 31 357.0, filed August 2, 1996 in Germany.

Applicants' amendment filed May 14, 2003, has been received and entered. Claims 14, 19, 38-51, 53, 56-59 and 65 have been amended. Claim 52 has been canceled. Claims 14-25, 27, 29, 38-51, 53-61, 65 and 66 are pending and currently under examination.

Priority

Acknowledgment is made of Applicant's intent to file a certified copy of the German application No: 196 31 357.0 (Applicant's amendment, top of page 9).

It is noted that the certified copy of the German application as required by 35 U.S.C. 119(b) has been filed (May 6, 2003).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-25, 27, 29, 38-61, 65 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Independent claims 14, 49-51, 53 and 65 have been amended to recite 'a non-transforming early papillomavirus polypeptide encoded by an early papillomavirus gene selected from the group consisting of E6-ORF, E7-ORF and fragments thereof'. Dependent claims 17, 19, 38-48 have been amended similarly to indicate that the non-transforming ORF is E6-ORF and/or E7-ORF. The claims are unclear in the recitation of "non-transforming" because neither E6 nor E7 are recognized to be transforming proteins. Applicants have argued that the art recognizes that these polypeptides contribute to the transformation of a cell in which they are expressed. Examiner would concede that expression of both proteins could lead to the transformation of a cell, however each singly are not considered transforming proteins. This interpretation is consistent with the references provided by Applicants wherein each of the E6 and E7 alone lead to the immortalizaton of a cell, not its transformation (see Liu *et al.*, supplied by Applicants in Appendix A). Further, while the activity of E6 and E7 are fairly well characterized in the prior art as demonstrated by Tommasino *et al.* (supplied by Applicants in Appendix A), these activities alone do not cause transforamtion and rely on the presence and activity of both E6 and E7. Additionally, as set forth in the previous office action upon review of the specification, there does not appear to be the specific teaching that E6 and E7 by themselves are transfroming proteins. Moreover, a review of the entire disclosure does not indicate that these ORF were considered transforming, nor if they were considered such, any teaching on how to modify these sequences to be "non-transforming". Further, it is noted that the claims as

amended recite expressing the entire ORF of E6 and E7, therefore are inconsistent with Applicants arguments that E6 and E7 are transforming. The metes and bounds of the claims are indefinite because the art recognizes that E6 and E7 alone are not transforming proteins. Alternatively, if one were to concede they are transforming proteins, it is unclear how one would practice the breadth of the claims as they encompass expressing the entire ORF. Finally, the transforming ability of the E6/E7 proteins depends on the type of cell in which it is expressed. The properties ascribed to the encoded proteins is indefinite because they are dependent on how the properties are assessed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-25, 27, 29, 38-61, 65 and 66 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Whittle *et al.* ('087), Donelly *et al.* ('785) and Johnson (96/00583) for reasons of record set forth in the previous office actions of June 13, 2002, paper number 24.

Applicants summarize the claimed invention and note that the invention encompassing expressing non-tranforming E6 and E7 ORFs (page 10). Applicants summarize the teaching of Swan *et al.* and the properties of E6 and E7 known in the art (page 11). Further, Applicants provide a definition of the properties of E6 and E7 as defined by "The Encyclopedia of Molecular Biology" (1994 supplied by Applicants in Appendix A) and argue that the properties of the proteins lead to the transformation of a cell (pages 11-12).

These arguments are not persuasive, because in each case it is the expression of both E6 and E7 that leads to the transformation. Examiner does not contest the well characterized properties of E6 and E7, however as illustrated in "The Encyclopedia of Molecular Biology" in the description of E6 and E7 the properties alone do cause transformation. Further, it should be noted that not all HPV strains provide such properties, for example E6 of only HPV 16 and 18 have the properties described in "The Encyclopedia of Molecular Biology". Finally, it is noted that the claims as amended broadly encompass expressing the entire E6/E7 ORFs from any strain of HPV in any cell. Again, Examiner would not contest the well characterized properties of E6 and E7 known in the prior art, however the art supports E6 and E7 alone lead to immortalization, and that the combination is required for transformation. Moreover, not every E6/E7 from any strain of HPV encompassed by the claims have such properties and the function would dependent

on the cell in which it is expressed. As summarized in the previous office action, the present specification teaches as a preferred polypeptide the "non-transforming" proteins encoded by the E6 and E7-ORFs (page 3, second full paragraph), clearly encompassing expressing the entire E6 and E7. A review of the entire disclosure does not indicate that these ORF were considered transforming, nor if they were considered such, any teaching on how to modify these sequences to be "non-transforming". Applicants' arguments are not found persuasive because the specification teaches the preferred use of E6 and E7 as non-transforming proteins in the context of the claimed invention, and the art recognizes E6 and E7 as non-transforming.

In addition, summarizing the teaching of each of the cited references, Applicants argue that Donelly *et al.* teaches away from using the AAV vectors disclosed in Johnson. Specifically, Applicants point to teachings in Donelly *et al.* that retroviral vectors have certain limitations which make them less suitable as a delivery vehicle for DNA vaccines and for the teaching of the preferred use of artificially engineered plasmids. With respect to Whittle *et al.* Applicants argue that no specific motivation for use of an AAV vector system is provided . Applicants argue that a *prima facie* case has not been established because the rejection fails to provide the motivation to combine the prior art references. See Applicants' amendment, pages 13-14. Applicants' arguments have been fully considered but not found persuasive.

With respect to Applicants arguments that Donelly *et al.* teaches away from the present invention, Examiner acknowledges the specific portions of Donelly *et al.* cited, however, none of these specifically teach away from the claimed invention. As noted in the previous rejection

Donelly *et al.* generally supports the use of any vector (see previous action paper number 24, pages 4-6). Examiner notes that plasmids are preferred embodiment taught by Donelly *et al.* because they do not replicate, however this does not teach away from the use of other vectors which do not replicate. Also, the limitations for the use of retroviruses is noted, however AAV is not a retrovirus (it is a replication deficient ssDNA parvorvirus), nor does it have the limitations set forth by Donelly *et al.* for a retrovirus vector. The teachings pointed to by Applicants provide a general knowledge of the art for various vectors which are known at the time of filing. At the time of filing, Johnson teaches that the AAV vectors were known and used for delivering DNA vaccines. An AAV vector is replication deficient which a solution to the problem acknowledged by Donelly *et al.* for the use of a retrovirus. Further, Johnson teaches the artisan is capable of removing all but the ITR for the insertion of heterologous sequences into an AAV genome. Finally, Johnson teaches the insertion of multiple and varied viral sequences which could serve in the context of a DNA vaccine. Applicants' arguments that Donelly *et al.* teaches away from the use of the AAV vectors of Johnson is not persuasive, because the use of AAV vectors in the context of DNA vaccines for various viruses was known, and the properties of AAV vectors solve problems recognized by the art as set forth in Donelly *et al.* for the use of retroviral vectors.

With respect to Applicants' arguments regarding that the references combined do not teach a **fused polypeptide** comprising a **non-transforming** E6/E7-ORF, it is noted that Whittle *et al.* specifically teaches an example of the fusion protein of HPV L2 and E7 (see summary in

abstract and column 5, lines 47-51). Further, as discussed above in detail, the E6 and E7 are non-transforming. Applicants arguments are not persuasive because there is the specific teaching of a L2-E7 fusion protein by Whittle *et al.* which anticipates the claims.

The basis of the present rejection relies on the teaching of Donnelly *et al.* for the overall teaching for DNA vaccines expressing HPV antigens and the teaching of Johnson for advantageous use of AAV vectors for DNA vaccines against viral antigens. Whittle *et al.* provides the specific teaching that at the time of filing HPV fusion proteins were used as vaccines and could be expressed by a vector. As noted in the previous office action, all of the references are related in the art as they are drawn to providing vaccines. More specifically, the references provide the necessary and specific teachings for the generation of HPV antigens administered as a DNA vaccine. The motivation for the combination of the references is to provide for an effective DNA vaccine, in this case the advantage of a non-replicating AAV vector which is capable of infecting all cell types in a subject for the delivery of known papilloma virus antigens to a subject. As indicated in the prior office action n this case there has been no reliance on common knowledge to make the instant rejection or conclusory statements for combining non-analogous art.

Thus, for the reasons above and of record, the claimed invention as a whole was clearly *prima facie* obvious, and therefore, the rejection is maintained.

Claims 16, 18, 20 and 50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Whittle *et al.* ('087), Donelly *et al.* ('785) and Johnson (96/00583) in further view of Gissmann *et al.* (96/11272) for reasons of record set forth in the previous office actions of June 13, 2002, paper number 24.

Claims 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Whittle *et al.* ('087), Donelly *et al.* ('785) and Johnson (96/00583) in further view of Stanley *et al.* ('869) for reasons of record set forth in the previous office actions of June 13, 2002, paper number 24.

Applicants do not specifically traverse the teaching of Gissmann *et al.* or Stanley *et al.* and argue only that the teachings do not remedy the deficiencies of Whittle *et al.* ('087), Donelly *et al.* ('785) and Johnson. See Applicants' amendment, bottom of page 14. Applicants' arguments have been fully considered but not found persuasive.

Gissmann *et al.* was relied upon to provide that at the time of filing that various HPV strains were known as well as the early and late ORFs. It is noted that Whittle *et al.* recognizes the existence of a variety of HPV strains (column 1, lines 40-45), however they do encompass all those recited in the instant claims. The reliance on Gissmann *et al.* was to provide evidence of what was well known in the art, in particular the specific HPV strains to make obvious each of the limitations in the claims. Applicants' arguments that the artisan would not combine Gissmann *et al.* because the fusion proteins generated are not the same as disclosed by Whittle *et al.* is unpersuasive because Gissmann *et al.* is not relied upon for this teaching.

Like Gissmann *et al.*, Stanley *et al.* is relied upon to teach what was known in the art, specifically that one or more immune system activators can be administered to augment the effectiveness of the vaccine. Stanley *et al.* teach that IL-12 can be administered with HPV antigens or a vector encoding said antigens (summarized in abstract). It is noted that Stanley *et al.* even cites Donnelly *et al.* as a means known in the art as polynucleotide vaccine (column 6, lines 65-67). Applicants arguments are not found persuasive because Stanley *et al.* relied upon only for teaching a more effective vaccine by providing IL-12 to a subject, and not required for the *prima facie* case over Whittle *et al.*, Donelly *et al.* and Johnson.

Thus, for the reasons above and of record, the claimed invention as a whole was clearly *prima facie* obvious, and therefore, the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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